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NOVEL COMPLEXES OF FATTY ACID ESTERS OF POLYHYDRIC HYDROXYALKANES AND PYRIDINE CARBOXY DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to chemical complexes and pharmaceutical compositions comprising a combination of a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative. Their therapeutic application as anti-microbial agents, such as a bactericidal or a fungicidal agent, or as agents for suppression of suppression of hypersensitivity and inflammatory reactions, is disclosed herein.

BACKGROUND OF THE INVENTION

Hypersensitivity is defined as a state of altered reactivity in which the body reacts with an exaggerated immune response to a substance (antigen). Hypersensitivity may be caused by exogenous or endogenous antigens. Hypersensitivity reactions underlie a large number of diseases. Among these, allergic and autoimmune conditions are of great importance. A classification of hypersensitivity diseases is given in the textbook Clinical Medicine (Kumar, P. and Clark, M.: "Clinical Medicine", 3rd edition, p. 147-150, 1994, Bailliere Tindall, London).

Type I hypersensitivity reactions (IgE mediated allergic reactions) are caused by allergens (specific exogenous antigens), e.g. pollen, house dust, animal dandruff, moulds, etc. Allergic diseases in which type I reactions play a significant role include asthma, eczema (atopic dermatitis), urticaria, allergic rhinitis and anaphylaxis.

Type II hypersensitivity reactions are caused by cell surface or tissue bound antibodies (IgG and IgM) and play a significant role in the pathogenesis of myasthenia gravis, Goodpasture's syndrome and Addisonian pernicious anaemia.

Type III hypersensitivity reactions (immune complex) are caused by autoantigens or exogenous antigens, such as certain bacteria, fungi and parasites. Diseases in which type III hypersensitivity reactions play a significant role include lupus erythematosus, rheumatoid arthritis and glomerulonephritis.

Type IV hypersensitivity reactions (delayed) are caused by cell or tissue bound antigens. This type of hypersensitivity plays a significant role in a number of conditions, e.g. graft-versus-host disease, leprosy, contact dermatitis and reactions due to insect bites.

Type I to type IV hypersensitivity reactions are all classically allergic reactions, which may lead to histamine release. However, hypersensitivity reactions are also those, where histamine release is triggered through the directly action of "triggering substances" with the cellular membrane. Examples of "triggering substances" are, but not limited to, toxins, food constituents and certain drugs.

A number of drug classes are available for the treatment of hypersensitivity reactions. Among these, the corticosteroids are some of the most widely used drugs. Corticosteroids primarily exert their pharmacological action by non-selectively inhibiting the function and proliferation of different classes of immune cells resulting in suppression of hypersensitivity reactions. Unfortunately, the corticosteroids are associated with a number of serious side effects, e.g. immunosuppression, osteoporosis and skin atrophy.

Cancer is caused by an uncontrolled proliferation of cells that express varying degrees of fidelity to their precursors. These cancer cells form a malignant tumour that enlarges and may spread to adjacent tissues or through blood and lymph systems to other parts of the body. There are numerous forms of cancer of varying severity. For most types of cancer there is no effective treatment today.

Niacinamide, which is also known as nicotinamide, has been found to be a potent inhibitor of poly(ADP-ribose)polymerase.
Poly(ADP-ribose)polymerase, also known as poly(ADP-ribose)synthetase or poly(ADP-ribose)transferase is an nuclear enzyme that catalyses the posttranslational modification of nuclear proteins by covalent attachment of ADP-ribosyl moieties derived from NAD^+ with an accompanying release of nicotinic acid amide. Preferred acceptor proteins are nuclear histones, whose poly-ADP-ribosylation induces local alterations in the architecture of chromatin domains.

Inhibitors of poly(ADP-ribose)polymerase have been found to suppress hypersensitivity reactions and inflammation.

A number of pathogenic bacteria and fungi play an essential role in the development of a plethora of skin diseases. For example, atopic dermatitis that is widely considered as an inflammatory skin disorder is often associated with secondary infections, e.g. with Staphylococcus Aureus, thus giving rise to aggravation of the symptoms. Similarly, the facial eczematous disease seborrhoeic dermatitis is associated with fungal derived infections, typically caused by Pityrosporum ovale.

Today, such skin diseases are often treated by combination of bactericides and fungicides although the diseases merely relate to inflammatory conditions than to infectious conditions. Moreover, antibiotics may also be suggested in treating such skin diseases, but today the topical application of traditional antibiotics is limited due to risk of developing resistant strains.

As recognised by the present inventor, there is a need for agents that provide combined anti-inflammatory and anti-microbial therapeutic effects in an efficient manner.

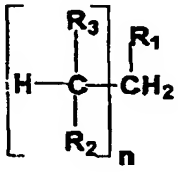
SUMMARY OF THE INVENTION

The present inventor has found that a combination of a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative significantly suppresses inflammatory reactions. Accordingly, the combination of a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative are of use generally in the immunomodulation of a mammal, such as a human. Furthermore, such combinations of components possess broad-spectrum antibacterial and fungicidal properties, thereby making them highly relevant for the treatment of a great number of infectious diseases and inflammatory skin diseases, including those diseases associated with secondary infections. The present inventor provides data herein demonstrating the anti-inflammatory properties of said combinations of components as well as their effect on suppression of multi-resistant bacteria (mithycillin resistant Staphylococcus aureus).

Contrarily to existing therapeutic agents, such as corticosteroids or non-steroidal anti-inflammatory drugs, the chemical complexes and pharmaceutical compositions according to the present invention have the advantage of not being likely to be associated with any serious side effects, as all of their components are non-toxic and well tolerated by the organism in the pharmacologically relevant doses.

Accordingly, the present invention provides a chemical complex or a pharmaceutical composition comprising:

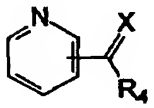
i) a fatty acid ester of a polyhydric hydroxyalkane according to formula I;



I

wherein n is 1, 2, 3, 4 or 5, at least one of the R_1, R_2 and R_3 is OOR' and at most two of the R_1, R_2 and R_3 is independently selected from H, OH, OM and OOR', wherein R' is selected from C_6-C_{20} alkyl and C_6-C_{20} alkenyl and isomers thereof; and OM is a salt; and

ii) an optionally substituted pyridine carboxy derivative or salts thereof according to formula II



II

wherein X is selected from O and S; R_4 is selected from OH; OR''; NH_2; NHR''; NR''R'''; O^-Y^+, and halogen, wherein R'' and R''' are independently selected from optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} alkoxyl and optionally substituted C_2-C_{20} alkenyl; and Y is a base addition salt of the free carboxylate.

The chemical complexes and pharmaceutical compositions according to the invention may be employed for therapeutic applications such as i) immunomodulation, ii) the treatment of hypersensitivity diseases; iii) the treatment of inflammatory diseases, iv) the treatment of IgE mediated allergic reactions and conditions; v) the treatment of autoimmune disorders; vi) the alleviation of pain; vii) the treatment of infectious diseases, e.g. bacterial or fungal infections; viii) the treatment of cancer.

An important aspect of the invention relates to the use of a combination of a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative for the preparation of a product for the immunomodulation of a mammal, such as a human, as well as to a method for immunomodulation in a mammal, such as a human, comprising the administration of an effective amount of a combination of a fatty acid ester of a polyhydric

hydroxyalkane and a pyridine carboxy derivative, or a complex comprising said combination to said mammal.

Another important aspect of the invention relates to the use of a combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative for the preparation of a medicament for anti-microbial treatment of a mammal, such as a human as well as to a method for the suppression of bacteria, fungi, vira and/or parasites in a mammal, such as a human, comprising the administration to said mammal an effective amount of a combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative, or a chemical complex comprising a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative.

Still further aspects relate to the immunomodulation activity of said combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative, for which reason said invention also relate to a method for the suppression of hypersensitivity and/or inflammatory reaction in a mammal; a method for the treatment of hypersensitivity and/or inflammatory skin diseases in general and particularly with respect to the treatment of pruritus, urticaria, of atopic eczema, contact dermatitis, seborrhoeic dermatitis, acne, rosacea, alopecia, vitiligo and/or psoriasis; a method for the treatment of IgE mediated allergic reaction in general and particularly with respect to asthma, allergic rhinitis, and/or anaphylaxis; a method for the treatment of autoimmune disease and/or chronic inflammatory disease in general and particularly with respect to diabetes, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout or osteoarthritis; a method for the treatment of cancer; and to a method for the alleviation of pain; each method comprising the administration of an effective amount of a combination of a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative, or a complex or composition comprising said combination to a mammal, such as a human.

DETAILED DESCRIPTION OF THE INVENTION

The present inventor provides data herein indicating that a combination of a fatty acid esters of polyhydric hydroxyalkanes reduces the inflammation in the arachidonic acid induced ear inflammation test model. The reduction was comparable to that of therapeutically relevant doses of betamethasone 17-valerate. Consequently, the combination of fatty acid esters of polyhydric hydroxyalkanes and pyridine carboxy derivate is effective in suppressing hypersensitivity and inflammatory reactions. Moreover, surprisingly, the present combinations according to the invention was proved to be effective in inhibiting the growth of a number of microorganisms, including Candida

Albicans, Epidermophyton floccosum, Microsporum canis, Streptococcus faecalis and Trichophyton rubrum. However, each of the individual tested components of the complex did not inhibited growth, for which reason the present combination of fatty acid esters of polyhydric hydroxyalkanes and pyridine carboxy derivate seems to have an synergistic effect with respect to suppression of microbial growth. Also very surprisingly, the present inventor found that combinations according to the invention inhibited the growth of resistant Staphylococcus Aureus.

Hence, the combination of a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative significantly suppresses hypersensitivity reactions and/or inflammatory reactions. Such chemical complexes are novel and provide a surprisingly good anti-hypersensitivity and anti-inflammatory effect with a surprisingly good safety profile. Simultaneously, the complexes of the invention provide strong antimicrobial effects, especially in topical application, with a surprisingly broad spectrum of activity against pathogenic bacteria and fungi and with a surprisingly low toxicity for humans providing an excellent safety profile. Thus the chemical complexes or compositions of the invention are virtually non-toxic and yet very therapeutically effective.

According to the invention, said combination of a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative may be provided in the form of a chemical complex. Without being limited to a particular theory, the combination is advantageous provided as a chemical complex for purposes of achieving homogeneous mixtures of the two agents, thereby positively affecting the resulting therapeutic effect. Furthermore, said combination of a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative may be provided as a pharmaceutical composition, dietary supplement or a cosmetic, wherein said combination may be in a chemical complex form or just mixtures of the two individual agents. In some embodiments thereof, said combination of a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative may each be provided in separate compositions.

Such combinations of fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative as well as compositions and chemical complexes of said combination are novel and provide a surprisingly effective anti-hypersensitivity and anti-inflammatory effect with a surprisingly good safety profile. Thus the chemical complexes or compositions of the invention are virtually non-toxic and yet very therapeutically effective.

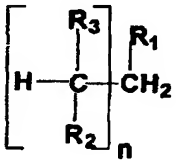
The present inventor proposes the hypothesis that the very advantageous therapeutic index of the combination of an fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative in comparison to the individual anti-hypersensitivity or

antimicrobial drugs is due to any synergistic effect or summarised effect between the components of the combinations. Thus, this results in a lower toxic load on the body in comparison to any single chemical compound, while still achieving a surprisingly good therapeutic effect.

The invention is based, at least in part, on the synergistic activity of the pyridine carboxy derivative with the fatty acid ester of a polyhydric hydroxyalkane in comparison to either component. This surprising synergism allows for the combining of any fatty acid ester of a polyhydric hydroxyalkane with an optionally substituted pyridine carboxy derivative to achieve the desired effect at much lower doses than ever anticipated. Moreover, the synergism allows for the use of a fatty acid ester of a polyhydric hydroxyalkanes or a pyridine carboxy derivative previously not used for the desired effect due to the high doses required to achieve said effect. Still further, this synergism allows for the use of compounds, which are not used due to the toxicity associated with therapeutically effective doses.

The present invention provides a chemical complex or a pharmaceutical composition comprising:

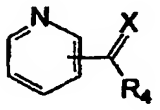
i) a fatty acid ester of a polyhydric hydroxyalkane according to formula I;



I

wherein n is 1, 2, 3, 4 or 5, at least one of the R_1, R_2 and R_3 is OOR' and at most two of the R_1, R_2 and R_3 is independently selected from H, OH, OM and OOR', wherein R' is selected from C_1-C_{20} alkyl and C_2-C_{20} alkenyl and isomers thereof; and OM is a salt; and

ii) an optionally substituted pyridine carboxy derivative or salts thereof according to formula II



II

wherein X is selected from O and S; R_4 is selected from OH; OR"; NH_2; NHR"; NR"R"', O^-Y^+, and halogen, wherein R" and R"' are independently selected from optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} alkoxyl and optionally substituted C_2-C_{20} alkenyl; and Y is a base addition salt of the free carboxylate.

The term "chemical complex" is intended to include the definition defined by IUPAC that read as follows:

"A molecular entity formed by loose association involving two or more component molecular entities (ionic or uncharged), or the corresponding chemical species. The bonding between the components is normally weaker than in a covalent bond." (IUPAC Compendium of Chemical Terminology 2nd Edition (1997))

Thus, the term "chemical complex" is intended to mean any combination of the component molecules. It is not intended necessarily to imple an ionic or otherwise association between the components. Also as used herein, the chemical complex of the present invention relates to a complex obtainable from the combining of a pyridine carboxy derivative of Formula II and a fatty acid ester of a polyhydric alkane of Formula I.

As mentioned, the pyridine carboxy derivative may optionally be substituted. The term "optionally substituted" is intended to mean the substitution of one or more hydrogen atoms is substituted with another atom, chemical group or entity, termed substituents. Illustrative examples of substituents include carboxyl, formyl, amino, hydroxyl, halogen, nitro, sulphono, sulphanyl, C1-6-alkyl, aryl, aryloxy, aryloxycarbonyl, arylcarbonyl, heteroaryl, amino, mono- and di(C1-6-alkyl)amino; carbamoyl, mono- and di(C1-6-alkyl)aminocarbonyl, amino-C1-6-alkyl-aminocarbonyl, mono- and di(C1-6-alkyl)amino-C1-6-alkyl-aminocarbonyl, C1-6-alkylcarbonylamino, cyano, guanidino, carbamido, C1-6-alkanoyloxy, C1-6-alkylsulphonyloxy, dihalogen-C1-6-alkyl, trihalogen-C1-6-alkyl, C1-6-alkoxyl, oxo, C1-6-carboxyl, C1-6-alkoxycarbonyl, C1-6-alkylcarbonyl,
where aryl and heteroaryl representing substituents may be substituted 1-5 times with C1-6-alkyl, C1-6-alkoxy, nitro, cyano, hydroxy, amino or halogen. In general, the above substituents may be susceptible to further optional substitution.

The term "C_1-C_{20} alkyl" is intended to mean a linear or branched saturated hydrocarbon chain wherein the longest chains has from one to twenty carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, undecacyl, dodecyl, etc. A branched hydrocarbon chain is intended to mean a C_1-C_{20} alkyl substituted at any carbon with a hydrocarbon chain. The C_1-C_{20} alkyl chain of the present invention may be optionally substituted.

The term "C_2-C_{20} alkenyl" is intended to mean a linear or branched unsaturated hydrocarbon chain with one or more double bindings and wherein the longest chains has from one to twenty carbon atoms. A branched hydrocarbon chain is intended to mean a C_1-C_{20} alkyl substituted at any carbon with a hydrocarbon chain. The C_2-C_{20} alkenyl chain of the present invention may be optionally substituted.

The term "C_1-C_{20} alkoxyl" is intended to mean a linear or branched hydrocarbon chain wherein the longest chains has from one to twenty carbon atoms, such as methoxy, ethoxyl, n-propoxyl, isopropoxyl, n-butoxyl, isobutoxyl, isopentoxyl, hexoxyl, heptoxyl, octoxyl, etc. A branched hydrocarbon chain is intended to mean a C_1-C_{20} alkyl substituted at any carbon with a hydrocarbon chain. The C_1-C_{20} alkyl chain of the present invention may be optionally substituted.

The term "halogen" includes fluorine, chlorine, bromine and iodine.

As stated, the esters according to formula I comprise at least one ester group, OOR', wherein R' is an alkyl or an alkenyl with a carbon chain length of at most 20 carbon atoms. However, in suitable embodiments of the invention, the R' are shorter than twenty carbon atoms or longer than one or two carbon atoms. Thus, in various separate embodiments R' is selected from C_3-C_{18} alkyl and C_3-C_{18} alkenyl; C_4-C_{16} alkyl and C_{43}-C_{16} alkenyl; C_4-C_{16} alkyl and C_{43}-C_{16} alkenyl; C_4-C_{16} alkyl and C_{43}-C_{16} alkenyl; C_6-C_{12} alkyl and C_6-C_{12} alkenyl; C_6-C_{10} alkyl and C_6-C_{10} alkenyl; C_2-C_{10} alkyl and C_2-C_{10} alkenyl; and C_4-C_{10} alkyl and C_4-C_{10} alkenyl.

As mentioned, the R1, R2 and R3 of formula I are independently selected from H, OH, OM and OOR', wherein OM is a salt. As used herein, such a salt is intended to mean any salt of a hydroxide group. That is to say, wherein the oxygen is negatively charged and the complementary positively charged ion is for example, sodium, potassium or ammonium.

Moreover, in suitable embodiments, at least one, but at most two of the R1, R2 and R3 is OH. In still further interesting embodiments thereof, at most two of the R1, R2 and R3 is OOR'. Thus, mono and di-esters of fatty acids and a polyhydric hydroxyalkane are

anticipated. In some embodiments thereof, two different fatty acids may be esterified to the polyhydric hydroxyalkane and in other embodiments the fatty acids are identical.

In some suitable embodiments, the group, OOR' is selected from the group consisting of n-caproic acid, n-caprylic acid, n-capric acid, n-lauric acid or n-myristic acid moieties.

The fatty acid ester of a polyhydric hydroxyalkane, for illustrative purposes, may be selected from the group consisting of Ethyleneglycyl-1-hexanoate, Ethyleneglycyl-1-(4-noneoate), Glyceryl-2-(5-ethyl-octanoate), Trimetylenglycyl-1-dodecanoate-2-dodecanoate, Trimetylenglycyl-1-octadecanoate-2-(5,7,9-heptadecatrienoate), 1,2,3,4-butantetraol-1-undecanoate-3-nonanoate, 1-ol-2,3-butylenglycyl-1-heptandecanoate-2-heptandecanoate, Propylenglycyl- 2-(3-metyl-decanoate), 1,2-butylenglycyl-1-hexanoate-2-hexanoate, Ethyleneglycyl-1-octanoate, Ethylenglycyl-1-octanoate-4-(3-ethyl-hexanoate, 1,2,3,4-butantetraol-1-hexadecanoate-(4-(2,4-diethyl-8-hexadecenoate), 1,2,3,4-butanetetraol-2-eicosatrienoate, Glyceryl-1-decanoate-2-decanoate, 1,4-butylenglycyl-1-octanoate, 1-ol-2,3-butylenglycyl-1-heptandecanoate-2-heptandecanoate, Propylenglycyl-1-undecanoate-2-undecanoate, Propylenglycyl-1-(7,10-octadecadienoate)-2-octanoate, Glyceryl-2-(8,11,14-eicosatrienoate), Ethylenglycyl-1-decanoate-2-hexanoate, Ethylenglycyl-1-(4-tetradecenoate), Glyceryl-1-octanoate-3-undecanoate, Glyceryl-1-(4-nonenoate)- 3-hexanoate, Trimetylglycyl-1-octanoate, Trimetylenglycyl-1-undecanoate, Propylenglycyl-1-hexanoate, Propylenglycyl- 2-(3-metyl-decanoate), 1,2-butylenglycyl-2-octanoate, 1,2-butylenglycyl-1-nonaoate-2-octanoate, 1,3-butylenglycyl-1-decanoate-3-octanoate, 2,3-butylenglycyl-2-dodecanoate, 2,3-butylenglycyl-2-octanoate-3-octanoate, Ethylenglycyl-1-(3,6-octadecadienoate)-2-octanoate, Ethylenglycyl-1-(8-metyl-3,6-octadecadienoate), Glyceryl-1-(4,6,10-eicosatrienoate)-2-(4,6,10-eicosatrienoate), Glyceryl-1-(8-octadecenoate)-3-heptanoate, Trimetylenglycyl-2-(4-metyl-2,8-eicosadienoate), Propylenglycyl-1-nonanoate, 1,2,3,4-butantetraol-1-decanoate, 1,2,3,4-butantetraol-1-hexadecanoate-(4-(2,4-diethyl-8-hexadecenoate), 1,2,3,4-butanetetraol-2-eicosatrienoate, 2,3-butylenglycyl-2-hexanoate, 1-ol-2,3-butylenglycyl-1-(4-metyl-hexanoate), 1-ol-2,3-butylenglycyl-1-(3-octenoate), 1,4-butylenglycyl-1-dodecanoate, 1,4-butylenglycyl-1-decanoate-4-decanoate, 1,2,3,4-butantetraol-2-(2-metyl-octanoate), 1,2,3,4-butantetraol-1-hexanoate-2-hexanoate, Glyceryl-2-(3,5,7-hexadecatrienoate), Glyceryl-1-octanoate, Glyceryl-2-octanoate, Glyceryl-2-octanoate, Glyceryl-1-octanoate-2-octanoate, Glyceryl-2-(3,5,7-hexadecatrienoate), Glyceryl-1-(3-ethyl-2-metyl-8,10-eicosadienoate)- 2-octanoate, Propylenglycyl-1-(2,4-ethyl-6-tetradecaenoate)-2-(8,12-hexadecaenoate), 1,2-butylenglycyl-1-decanoate, 1,2-butylenglycyl-1-heptadecanoate-2-(4,8-heptadecadienoate), 1,2-butylenglycyl-1-(8-ethyl-4-metyl-6,16-octadecadienoate), Glyceryl-1-(5,8,11,14,17-eicosapentaenoate), Propylenglycyl-1-nonanoate-2-decanoate,

Trimetylenglycyl-1-octanoate-2-(4-ethyl-decanoate), 1,3-butylenglycyl-1-undecanoate, 1,3-butylenglycyl-3-hexanoate, 1,3-butylenglycyl-1-octanoate-3-octanoate, 1-ol-2,3-butylenglycyl-1-undecanoate-2-undecanoate, 1-ol-2,3-butylenglycyl-1-(2-ethyl-nonanoate)-2-hexanoate, Glyceryl-2-octanoate, Glyceryl-1-octanoate-2-octanoate, 1,4-butylenglycyl-1-octanoate-4-heptanoate, 2,3-butylenglycyl-2-dodecanoate-3-heptanoate, 1,2,3,4-butantetraol-2-(2-metyl-octanoate), 1,2,3,4-butantetraol-1-hexanoate-2-hexanoate, 1,4-butylenglycyl-1-(6,10,12,18-tetradecantetraenoate)-4-(4,8-dimetyl-6,13-eicosadienoate), 1,4-butylenglycyl-1-(2-ethyl-octanoate)-4-(4-nonenoate), Glyceryl-1-octanoate, Glyceryl-1-(5,8,11,14,17-eicosapentaenoate), Glyceryl-2-(8,11,14-eicosatrienoate), 1,2,3,4-butantetraol-2-(2-metyl-octanoate), Ethyleneglycyl-1-octanoate, Ethylenglycyl-1-octanoate-4-(3-ethyl-hexanoate), Glyceryl-1-octanoate, Glyceryl-1-(5,8,11,14,17-eicosapentaenoate), Glyceryl-2-(8,11,14-eicosatrienoate), Glyceryl-2-(8,11,14-eicosatrienoate), 1,2,3,4-butantetraol-2-(2-metyl-octanoate), Glyceryl-1-octanoate, Trimetylenglycyl-2-(4-metyl-2,8-eicosadienoate), Propylenglycyl-1-nonanoate, Glyceryl-1-(5,8,11,14,17-eicosapentaenoate), Propylenglycyl-1-(2,4-ethyl-6-tetradecaenoate)-2-(8,12-hexadecaenoate), 1,2-butylenglycyl-1-decanoate, 1,2-butylenglycyl-2-octanoate, Glyceryl-2-octanoate, 1,4-butylenglycyl-1-decanoate-4-decanoate, Glyceryl-2-octanoate, Ethylenglycyl-1-decanoate-2-hexanoate, 1-ol-2,3-butylenglycyl-1-(2-ethyl-nonanoate)-2-hexanoate, Glyceryl-2-(8,11,14-eicosatrienoate), derivatives and salts thereof.

As used herein, the pyridine carboxy derivative includes salts of compounds of formula II. The salts may be any pharmaceutically acceptable salt including hydrates, solvent addition forms, acid addition salts. In different embodiments of the invention, the salt is a hydriodide, hydrochloride or a hydrobromide, e.g. nicotinamide hydriodide.

The term "base addition salts" include alkali metals, such as sodium and potassium, alkali earth metals, such as calcium and magnesium, and organic addition salts such as quaternary ammonium cations.

As stated, the complex comprises, in part, the optionally substituted pyridine carboxy derivative according to Formula 2 wherein R_4 may be selected from OH; OR"; NH2; NHR"; NR"R'", O-Y+, and halogen. R" and R'" may independently be selected from optionally substituted C1-C20 alkyl, optionally substituted C_1-C_{20} alkoxyl and optionally substituted C_2-C_{20} alkenyl. In suitable embodiments, the carbon chain length of R' and R" are shorter than twenty carbon atoms, e.g. from C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_4 or C_1-C_3. With respect to the optionally substituted alkenyls, the carbon chain length is at least two carbon. Thus, the optionally substituted alkenyls can have any length, e.g. from C_2-C_{12} C_2-C_{10}, C_2-C_8, C_2-C_6, C_2-C_4 or C_2-C_3.

The optionally substituted pyridine carboxy derivative may, for illustrative purposes, be selected from the group consisting of optionally substituted nicotinic acid, its corresponding acyl halide, ester, acid salt, or amide, nicotinamide; optionally substituted isonicotinic acid, its corresponding acyl halide, ester, acid salt, or amide, isonicotinamide; and optionally substituted picolinic acid, its corresponding acyl halide, ester, acid salt, or amide, picolinamide.

In very interesting embodiments of the invention, the pyridine carboxy derivative is pyridine-3-carboxy derivative. Hence, in different embodiments of the invention, the pyridine carboxy derivative is selected from the group consisting of niacinamide, thioniacinamide, 6-aminoniacinamide, N2-methyl-niacinamide, N2-ethyl-niacinamide, nicotinic acid and inositol hexaniacinate or derivatives thereof. As stated above, these pyridine carboxy derivatives may optionally be further substituted or they may be provided as salts. In some embodiments, the pyridine ring may be substituted with an amino group or alkoxy group.

In the embodiment where the optionally substituted pyridine carboxy derivative is an amide, the amide may be its free primary amide (NH2), its secondary amide (NHR') or its tertiary amide (NR'R'').

As stated, the pyridine carboxy derivative may be optionally substituted. In one suitable embodiment, the pyridine carboxy is further substituted with a carboxy group such as a carboxylic acid. Moreover, in interesting embodiments the pyridine carboxy is further substituted with alkoxyl, e.g. methoxy and ethoxy, amino, acyl, halide, carboxylic ester, or acetamide. The pyridine carboxy may be substituted 0 to 4 times, such as 0, 1, 2, 3, or 4 times, preferably 0 to 1 time, most preferably 0 times. In one embodiment thereof the pyridine carboxy derivative is 6-amino-nicotinamide or 6-methoxy-nicotinamide.

In a suitable embodiment of the invention, the chemical complex and the composition comprises more than one pyridine carboxy derivative.

As stated, the complex comprises, in part, the fatty acid ester of a polyhydric hydroxyalkane. In a suitable embodiment of the invention, the chemical complex and the composition comprises more than one fatty acid ester of a polyhydric hydroxyalkane.

As stated the combination of the two agents provides a surprisingly effective therapeutic agent for suppression of hypersensitivity and inflammatory reactions. The proper

therapeutic efficacy may, in part, be adjusted by providing the two agents in suitable molar ratios or mass ratios.

Hence, the combination of a fatty acid ester of a polyhydric hydroxyalkane and the pyridine carboxy derivative in a chemical complex or in a compositions according to the invention comprises adjustable molar ratio's between fatty acid ester of a polyhydric hydroxyalkane and the pyridine carboxy derivative in the range of about 1:10000 to 10000:1. Preferably in the range of about 1:1000 to 1000:1, such as about 1:500 to 500:1, such as 1:100 to 100:1, about 1:50 to 50:1, or about 1:40 to 40:1, also about 1:30 to 30:1, such as about 1:25 to 25:1, about 1:20 to 20:1, about 1:18 to 18:1, about 1:16 to 16:1, about 1:14 to 14:1, or about 1:12 to 1:12, also about 1:10 to 10:1, such as about 1:9 to 9:1, about 1:8 to 8:1, about 1:7 to 7:1, about 1:6 to 6:1, also from 1:5 to 5:1, such as from 1:4 to 4:1, e.g. from 1:3 to 3:1, such as from 1:2 to 2:1.

Alternatively defined, the ratio between the fatty acid ester of a polyhydric hydroxyalkane and the pyridine carboxy derivative may be expressed as a mass ratio. The mass ratio between the fatty acid ester of a polyhydric hydroxyalkane and the pyridine carboxy derivative may be about 1:10000 to 10000:1, preferably about 1:1000 to 1000:1, such as about 1:500 to 500:1, such as 1:100 to 100:1, about 1:50 to 50:1, or about 1:40 to 40:1, also about 1:30 to 30:1, such as about 1:25 to 25:1, about 1:20 to 20:1, about 1:18 to 18:1, about 1:16 to 16:1, about 1:14 to 14:1, or about 1:12 to 1:12, also about 1:10 to 10:1, such as about 1:9 to 9:1, about 1:8 to 8:1, about 1:7 to 7:1, about 1:6 to 6:1, also from 1:5 to 5:1, such as from 1:4 to 4:1, e.g. from 1:3 to 3:1, such as from 1:2 to 2:1.

For the administration to a mammal, such as a human, the chemical complex may be administered directly, eventually provided in a capsule or the like. More convenient, the complex may be formulated into a composition comprising the chemical complex and optionally, one or more acceptable excipients. Alternatively, the combination of the two agents may also be formulated into a composition without being provided as a chemical complex. Thus, in some embodiments of the invention, the chemical complexes or compositions further comprises one of more excipent(s) or carrier(s), preferably pharmaceutically acceptable excipent(s) or carrier(s).

According to the invention, the above-mentioned chemical complexes or compositions may be combined with any other therapeutically active agents in order to strengthen, improve, potentiate, or prolong the therapeutic actions of said complexes and said compositions. Thus according to the invention, the composition may further comprise one or more therapeutically active agents. Therapeutically active agents of interest include those

selected from the group consisting of antioxidants, steroids, antibiotics, anti-inflammatory agents and NSAID's.

The compositions according to the present invention may be formulated for oral, topical, transdermal, or parenteral administration, preferably oral or topical administration. The compositions according to the present invention may be formulated as a pharmaceutical composition for oral, topical, transdermal, or parenteral administration, preferably oral or topical administration.

In a suitable embodiment of the invention, the compositions are used for oral administration. In another suitable embodiment of the invention the compositions are used for topical administration.

In a preferred embodiment of the invention the compositions are formulated for topical administration (e.g. to the skin) in the form of emulsions (e.g. creams or lotions), gels, solutions, liniments, ointments, sprays, aerosols or powders.

The fatty acid ester of a polyhydric hydroxyalkane and the pyridine carboxy derivative may together be comprised in a single formulation or may each individually be comprised in separate formulations. The separate formulations may be administered in a simultaneous or non-simultaneous manner. As stated, the fatty acid ester of a polyhydric hydroxyalkane and the pyridine carboxy derivative are together comprised in a single formulation.

The active ingredients of the chemical complex or pharmaceutical composition of the present invention need not be administered as one pharmaceutical entity, but may of course be administered as individual compounds or pharmaceutical compositions.

In addition to the formulations described previously, the compositions of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions for oral, topical, transdermal, or parenteral administration may be in form of, e.g., solid, semi-solid or fluid compositions and formulated according to conventional pharmaceutical practice, see, e.g., "Remington: The science and practice of pharmacy" 20th ed. Mack Publishing, Easton PA, 2000 ISBN 0-

912734-04-3 and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J. & J. C. Boylan, Marcel Dekker, Inc., New York, 1988 ISBN 0-8247-2800-9.

The choice of pharmaceutically acceptable excipients in a composition for use according to the invention and the optimum concentration thereof is determined on the basis of the selection of the Fatty acid ester of a polyhydric hydroxyalkane, selection of the pyridine carboxy derivative, the kind of dosage form chosen and the mode of administration. However, a person skilled in the art of pharmaceutical formulation may find guidance in e.g., "Remington: The science and practice of pharmacy" 20th ed. Mack Publishing, Easton PA, 2000 ISBN 0-912734-04-3. A pharmaceutically acceptable excipient is a substance, which is substantially harmless to the individual to which the composition will be administered. Such an excipient suitably fulfils the requirements given by the national drug agencies. Official pharmacopeias such as the British Pharmacopeia, the United States of America Pharmacopeia and the European Pharmacopeia set standards for well-known pharmaceutically acceptable excipients.

For topical, trans-mucosal and trans-dermal compositions, such as administration to the mucosa or the skin, the compositions for use according to the invention may contain conventional non-toxic pharmaceutically acceptable carriers and excipients including microspheres and liposomes.

The topical, trans-mucosal and trans-dermal compositions for use according to the invention include an array of solid, semi-solid and fluid compositions. Compositions of particular relevance are e.g. pastes, ointments, hydrophilic ointments, creams, gels, hydrogels, solutions, emulsions, suspensions, lotions, liniments, resoriblets, suppositories, enema, pessaries, moulded pessaries, vaginal capsules, vaginal tablets, shampoos, jellies, soaps, sticks, sprays, powders, films, foams, pads, sponges (e.g. collagen sponges), pads, dressings (such as, e.g., absorbent wound dressings), drenches, bandages, plasters and transdermal delivery systems.

The pharmaceutically acceptable excipients for topical, trans-mucosal and trans-dermal compositions may include solvents, buffering agents, preservatives, humectants, chelating agents, antioxidants, stabilizers, emulsifying agents, suspending agents, gel-forming agents, ointment bases, suppository bases, penetration enhancers, perfumes, skin protective agents, diluents, disintegrating agents, binding agents, lubricants and wetting agents.

The oral compositions for use according to the invention include an array of solid, semi-solid and fluid compositions. Compositions of particular relevance are e.g. solutions,

suspensions, emulsions, uncoated tablets, immediate-release tablets, modified-release tablets, gastro-resistant tablets, orodispersible tablets, efferverscent tablets, chewable tablets, soft capsules, hard capsules, modified-release capsules, gastro-resistant capsules, uncoated granules, effervescent granules, granules for the preparation of liquids for oral use, coated granules, gastro-resistant granules, modified-release granules, powders for oral adminstration and powders for the preparation of liquids for oral use.

The pharmaceutically acceptable excipients may include solvents, buffering agents, preservatives, humectants, chelating agents, antioxidants, stabilizers, emulsifying agents, suspending agents, gel-forming agents, diluents, disintegratig agents, binding agents, lubricants, coating agents and wetting agents.

Typical solvents may be selected from the group comprising water, alcohols, vegetable or marine oils (e.g. edible oils like almond oil, castor oil, cacao butter, coconut oil, corn oil, cottonseed oil, linseed oil, olive oil, palm oil, peanut oil, poppyseed oil, rapeseed oil, sesame oil, soybean oil, sunflower oil, and teaseed oil), mineral oils, fatty oils, liquid paraffin, polyethylene glycols, propylene glycols, glycerol, liquid polyalkylsiloxanes; and mixtures thereof.

Typical buffering agents may be selected from the group comprising of citric acid, acetic acid, tartaric acid, lactic acid, hydrogenphosphoric acid, diethylamine etc.

Typical preservatives may be selected from the group comprising parabens, such as methyl, ethyl, propyl p-hydroxybenzoate, butylparaben, isobutylparaben, isopropylparaben, potassium sorbate, sorbic acid, benzoic acid, methyl benzoate, phenoxyethanol, bronopol, bronidox, MDM hydantoin, Iodopropynyl butylcarbamate, EDTA, benzalconium chloride, and benzylalcohol, or mixtures of preservatives.

Typical humectants may be selected from the group comprising glycerin, propylene glycol, sorbitol, lactic acid, urea, and mixtures thereof. Typical chelating agents are but not limited to sodium EDTA and citric acid. Typical antioxidants may be selected from the group comprising butylated hydroxy anisole (BHA), ascorbic acid and derivatives thereof, tocopherol and derivatives thereof, cysteine, and mixtures thereof. Suitable emulsifying agents may be selected from the group comprising naturally occurring gums, e.g. gum acacia or gum tragacanth; naturally occurring phosphatides, e.g. soybean lecithin; sorbitan monooleate derivatives; wool fats; wool alcohols; sorbitan esters; monoglycerides; fatty alcohols, fatty acid esters (e.g. triglycerides of fatty acids); and mixtures thereof.

Suitable suspending agents may be selected from the group comprising celluloses and cellulose derivatives such as, e.g., carboxymethyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carrageenan, acacia gum, arabic gum, tragacanth, and mixtures thereof.

Suitable gel bases and viscosity-increasing components may be selected from the group comprising liquid paraffin, polyethylene, fatty oils, colloidal silica or aluminium, zinc soaps, glycerol, propylene glycol, tragacanth, carboxyvinyl polymers, magnesium-aluminium silicates, Carbopol®, hydrophilic polymers such as, e.g. starch or cellulose derivatives such as, e.g., carboxymethylcellulose, hydroxyethylcellulose and other cellulose derivatives, water-swellable hydrocolloids, carragenans, hyaluronates (e.g. hyaluronate gel optionally containing sodium chloride), and alginates including propylene glycol alginate.

Typical ointment bases may be selected from the group comprising beeswax, paraffin, cetanol, cetyl palmitate, vegetable oils, sorbitan esters of fatty acids (Span), polyethylene glycols, and condensation products between sorbitan esters of fatty acids and ethylene oxide, e.g. polyoxyethylene sorbitan monooleate (Tween).

Typical hydrophobic ointment bases may be selected from the group comprising paraffins, vegetable oils, animal fats, synthetic glycerides, waxes, lanolin, and liquid polyalkylsiloxanes. Typical hydrophilic ointment bases are but not limited to solid macrogols (polyethylene glycols).

Suitable powder components may be selected from the group comprising alginate, collagen, lactose, powder, which is able to form a gel when applied to a wound (absorbs liquid/wound exudate).

Suitable diluents and disintegrating agents may be selected from the group comprising lactose, saccharose, emdex, calcium phosphates, calcium carbonate, calcium sulphate, mannitol, starches and microcrystaline cellulose.

Suitable binding agents may be selected from the group comprising saccharose, sorbitol, gum acacia, sodium alginate, gelatine, starches, cellulose, sodium carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone and polyetyleneglycol.

Typical wetting agents may be selected from the group comprising sodium laurylsulphate and polysorbate 80.

Suitable lubricants may be selected from the group comprising talcum, magnesium stearate, calcium stearate, silicium oxide, precirol and polyethylenglycol.

Suitable coating agents may be selected from the group comprising hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpropylidone, ethylcellulose and polymethylacrylates.

Typical suppository bases may be selected from the group comprising oleum cacao, adeps solidus and polyethylenglycols.

The present inventor has recognised the therapeutic effect of the complexes and compositions of this invention, partly by observing the reduced inflammation of the arachidonic acid induced inflamed mouse ear upon administering the complexes and compositions. This test model is a commonly employed method for screening and evaluation of anti-inflammatory drugs.

The anti-inflammatory activity was demonstrated in the TPA induced ear inflammation test in mice, which is a commonly employed method for screening and evaluation of antiinflammatory drugs. This model has broad relevance to inflammatory reactions that occur in various hypersensitivity, allergic and autoimmune diseases. Furthermore TPA is known to induce cancer in mice and substances that inhibit TPA induced inflammation thus also inhibit the formation of cancer.

Thus, in a broadly sense the chemical complexes or compositions provides an immunomodulating effect. Moreover, the inventor has recognised that a number of diseases or conditions with similarities in the etiology of the inflammatory reactions that are provoked in the arachidonic acid induced inflamed mouse ear may be effectively treated by the present complexes and compositions of the invention. Such diseases and conditions relate in general to those associated with hypersensitivity reactions and inflammatory reactions. In a more specific sense, the chemical complexes or compositions of the invention provides suppression of hypersensitivity reactions, suppression of inflammatory reactions, suppression of IgE mediated allergic reactions, suppression of autoimmune reactions, reduction of pain, and suppression of cancer.

Hence, a further aspect of the invention relates to a method for immunomodulation in a mammal, such as a human, comprising the administration to said mammal of an effective amount of a combination of a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative, or a chemical complex comprising a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative.

As used herein, the term "effective amount" relates to the effective dose to be determined by a qualified practitioner, who may titrate dosages to achieve the desired response. Factors for consideration of dose will include potency, bioavailability, desired pharmacokinetic/pharmacodynamic profiles, condition of treatment, patient-related factors (e.g. weight, health, age, etc.), presence of co-administered medications (e.g., anticoagulants), time of administration, or other factors known to a medical practitioner.

As used herein, the "term treatment" relates to treatment of symptoms or prevention the relapse of symptoms in a person diagnosed with a disease related to inflammation, hypersensitivity, infection, cancer and/or pain.

A still further aspect relates to a method of suppression of bacteria, fungi, vira or parasites in a mammal, such as a human, comprising the administration to said mammal an effective amount of a combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative, or a chemical complex comprising a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative.

As stated the complexes and compositions according to the invention may be applicable for the preparation of a medicament. Thus, other aspects of the invention relates to the use of a combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative for the preparation of a medicament for the immunomodulation of a mammal, such as a human. Furthermore, another aspect of the invention relates to the use of a combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative for the preparation of a medicament for anti-microbial treatment of a mammal, such as a human.

As recognised by the present inventor, the method of immunomodulation and the providing of suppression of bacteria, fungi, vira or parasites in a mammal by administering said complexes or compositions of the invention or by the preparation of said medicament for use in such a method, further relates to methods and uses in the suppression of hypersensitivity reactions, suppression of inflammatory reactions, suppression of IgE mediated allergic reactions, suppression of autoimmune reactions, suppression of infections, reduction of pain, and/or suppression of cancer.

For illustrative purposes, the treatment of autoimmune disorders relates to the treatment of Autoimmune hepatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Autoimmune hemolytic anemias, Grave's disease, Myasthenia gravis, Type 1 Diabetes Mellitus, Inflammatory myopathies, Multiple sclerosis, Hashimoto's thyreoiditis,

Autoimmune adrenalitis, Crohn's Disease, Ulcerative Colitis, Glomerulonephritis, Progressive Systemic Sclerosis (Scleroderma), Sjögren's Disease, Lupus Erythematosus, Primary vasculitis, Rheumatoid Arthritis, Juvenile Arthritis, Mixed Connective Tissue Disease, Psoriasis, Pemfigus, Pemfigoid, and Dermatitis Herpetiformis.

The therapeutic action of the complexes and compositions of the invention may be relevant to diseases associated with hypersensitivity reactions or inflammation in general. Particularly, the treatment of hypersensitivity relates to the treatment of infections (viral, bacterial, fungal, parasitic), cold and flu, contact dermatitis, insect bites, allergic vasculitis, post-operative reactions, transplantation rejection (graft-versus-host disease), and so forth.

Treatment of IgE mediated allergic reaction or condition relates to the treatment of asthma, eczema (e.g. atopic dermatitis), urticaria, allergic rhinitis and anaphylaxis.

Moreover, the chemical complex or composition of the present invention may be used in a method for the treatment or prevention of any condition associated with pain. The applicant proposes the hypothesis that the therapeutic action is related to immunomodulation, possibly to a suppressing effect on hypersensitivity reactions.

As mentioned, a still further aspect of the invention relates to the treatment of infections comprising administration of the chemical complexes or compositions of the invention to a mammal, preferably to a human. A broad spectrum of antibacterial, antifungal, antiviral and antiparasital effects can be anticipated. Relevant but non-limiting examples of target organisms include: gram positive bacteria e.g. Baccillus subtilis, Brevibacterium ammoniagenes, Corynebacterium minutissimum, Enterococcus faecalis, Enterococcus faecalis, Micrococcus luteus, Mycobacterium phlei, Mycobacterium ranae, Staphylococcus aureus, Staphylococcus aureus, Staphylococcus aureus (Methicillin Resistant), Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus faecalis, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pneumoniae, Streptococcus pneumoniae; gram negative bacteria e.g. Enterobacter cloacae, Escherichia coli, Escherichia coli, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhimurium, Serratia marcescens; anaerobes e.g. Actinomyces viscosus, Bacteroides fragilis, Clostridium sporogenes, Corynebacterium acnes, Helicobacter pylori; fungi e.g. Aspergillus fumigatus, Candida albicans, Candida glabrata, Crytococcus neoformans, Epidermophyton floccosum, Exophiala jeanselmei, Microsporum canis, Microsporum gypseum, Trichophyton mentagrophytes, Trichophyton rubrum, Aspergillus niger, Cladosporium argillaceum, Mucor hiemalis, Mucor pusillus, Paecilomyces

varioti, Penicillum chrysogenum, Penicillum citrinum, Pityrosporum ovale, Rhizopus nigricans and Saccharomyces cerevisiae.

Accordingly, the complexes or compositions of the invention are particularly suitable for the treatment of inflammatory skin diseases associated with secondary infections, e.g. seborrhoeic dermatitis, atopic dermatitis, acne, rosacea, psoriasis, etc. Such secondary infections may often occur in association with any inflammatory condition of the skin or mucous membranes.

Moreover, the chemical complexes or compositions of the invention are suitable for the treatment or prevention of diseases caused by inflammation of various tissues, such as the inflammation of the prostate, in particular prostatitis. The complexes and compositions of the invention are also suitable for the treatment or prevention of diseases associated with inflammation, pruritus (itch), erythema or hyperproliferation of the skin especially when topical administration is employed.

Furthermore, immunomodulation relates to the treatment of autoimmune disease and/or chronic inflammatory disease, at least in part, for the treatment or prevention of diabetes, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout or osteoarthritis.

Still further, the chemical complexes or compositions of the invention may be employed for the treatment or prevention of cancer of any type and at any stage. The present inventor puts forward the hypothesis that the anticancer effect is due to a combination of immunomodulating and tumour-suppressing effects of the complexes and compositions of the invention.

EXAMPLES

The following examples describe the preparation of chemical complexes of the present invention.

General method examples 1-100:

The fatty acid mono- or di-esters of a polyhydric hydroxyalkane and the pyridine carboxy derivative are dissolved in as little solvent as possible. The solvent is removed by spray drying or freeze-drying. After the solvent is removed the product is a white to yellowish paste or powder.

The solvent is water:acetone in any v/v % combination.

The paste or powder is suitable for any type of product e.g. pharmaceutical products, dietary supplements and cosmetic formulations. Non-limiting examples of such products are tablets, capsules, ointments and lotions as described above.

Examples 1 to 10: Molar ratio fatty acid mono- or di-esters of a polyhydric hydroxyalkane/ pyridine carboxy derivative 1:10000 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 1 mol.	Pyridine carboxy derivative 10000 mol.
Example 1.	Ethyleneglycyl-1-hexanoate	Niacinamide
Example 2.	Ethyleneglycyl-1-(4-noneoate)	Niacinamide
Example 3.	Glyceryl-1-heptanoate	N2-methyl-niacinamide
Example 4.	Glyceryl-2-(5-ethyl-octanoate)	N2-ethyl-niacinamide
Example 5.	Trimethylenglycyl-1-dodecanoate-2-dodecanoate	Aminoniacinamide
Example 6.	Trimethylenglycyl-1-octadecanoate-2-(5,7,9-heptadecatrienoate)	Thioniacinamide
Example 7.	1,2,3,4-butantetraol-1-undecanoate-3-nonanoate	Aminoniacinamide
Example 8.	1-ol-2,3-butylenglycyl-1-heptandecanoate-2-heptandecanoate	Niacinamide
Example 9.	Propylenglycyl- 2-(3-methyl-decanoate)	N2-methyl-niacinamide
Example 10.	1,2-butylenglycyl-1-hexanoate-2-hexanoate	Niacinamide

Examples 11 to 20: Molar ratio Fatty acid mono- or di-esters of a polyhydric hydroxyalkane / pyridine carboxy derivative 1:5000 (mol/mol).

	Fatty acid mono- or di-esters of a	Pyridine carboxy derivative

	polyhydric hydroxyalkane 1 mol.	5000 mol.
Example 11.	Ethyleneglycyl-1-octanoate	Niacinamide
Example 12.	Ethylenglycyl-1-octanoate-4-(3-ethyl-hexanoate	Thioniacinamide
Example 13.	1,2,3,4-butantetraol-1-hexadecanoate-(4-(2,4-diethyl-8-hexadecenoate)	Thioniacinamide
Example 14.	1,2,3,4-butanetetraol-2-eicosatrienoate	Aminoniacinamide
Example 15.	Glyceryl-1-decanoate-2-decanoate	Niacinamide
Example 16.	1,4-butylenglycyl-1-octanoate	N2-methyl-niacinamide
Example 17.	1-ol-2,3-butylenglycyl-1-heptandecanoate-2-heptandecanoate	N2-methyl-niacinamide
Example 18.	Propylenglycyl-1-undecanoate-2-undecanoate	Aminoniacinamide
Example 19.	Propylenglycyl-1-(7,10-octadecadienoate)-2-octanoate	Niacinamide
Example 20.	Glyceryl-2-(8,11,14-eicosatrienoate)	N2-methyl-niacinamide

Examples 21 to 30: Molar ratio Fatty acid mono- or di-esters of a polyhydric hydroxyalkane / pyridine carboxy derivative 1:1000 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 1 mol.	Pyridine carboxy derivative 1000 mol.
Example 21.	Ethylenglycyl-1-decanoate-2-hexanoate	Niacinamide
Example 22.	Ethylenglycyl-1-(4-tetradecenoate)	Niacinamide
Example 23.	Glyceryl-1-octanoate-3-undecanoate	N2-methyl-niacinamide
Example 24.	Glyceryl-1-(4-nonenoate)- 3-hexanoate	N2-ethyl-niacinamide
Example 25.	Trimethylglycyl-1-octanoate	Aminoniacinamide
Example 26.	Trimethylenglycyl-1-undecanoate	Thioniacinamide
Example 27.	Propylenglycyl-1-hexanoate	Aminoniacinamide
Example 28.	Propylenglycyl- 2-(3-methyl-decanoate)	Niacinamide
Example 29.	1,2-butylenglycyl-2-octanoate	N2-methyl-niacinamide
Example 30.	1,2-butylenglycyl-1-nonaoate-2-octanoate	Niacinamide

Examples 31 to 40: Molar ratio Fatty acid mono- or di-esters of a polyhydric hydroxyalkane/ pyridine carboxy derivative 1:500(mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 1 mol.	Pyridine carboxy derivative 216 mol.
Example 31.	1,3-butylenglycyl-1-decanoate-3-octanoate	Aminoniacinamide

Example 32.	2,3-butylenglycyl-2-dodecanoate	Niacinamide
Example 33.	2,3-butylenglycyl-2-octanoate-3-octanoate	Thioniacinamide
Example 34.	Ethylenglycyl-1-(3,6-octadecadienoate)-2-octanoate	Niacinamide
Example 35.	Ethylenglycyl-1-(8-methyl-3,6-octadecadienoate)	N2-ethyl-niacinamide
Example 36.	Glyceryl-1-(4,6,10-eicosatrienoate)-2-(4,6,10-eicosatrienoate)	Thioniacinamide
Example 37.	Glyceryl-1-(8-octadecenoate)-3-heptanoate	Niacinamide
Example 38.	Trimethylenglycyl-2-(4-methyl-2,8-eicosadienoate)	Niacinamide
Example 39.	Propylenglycyl-1-nonanoate	N2-ethyl-niacinamide
Example 40.	1,2,3,4-butantetraol-1-decanoate	Thioniacinamide

Examples 41 to 50: Molar ratio Fatty acid mono- or di-esters of a polyhydric hydroxyalkane/ pyridine carboxy derivative 1:100 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 1 mol.	Pyridine carboxy derivative 100 mol,
Example 41.	1,2,3,4-butantetraol-1-hexadecanoate-(4-(2,4-diethyl-8-hexadecenoate)	Niacinamide
Example 42.	1,2,3,4-butanetetraol-2-eicosatrienoate	Thioniacinamide
Example 43.	2,3-butylenglycyl-2-hexanoate	N2-methyl-niacinamide
Example 44.	1-ol-2,3-butylenglycyl-1-(4-methyl-hexanoate)	N2-ethyl-niacinamide
Example 45.	1-ol-2,3-butylenglycyl-1-(3-octenoate)	Thioniacinamide
Example 46.	1,4-butylenglycyl-1-dodecanoate	Aminoniacinamide
Example 47.	1,4-butylenglycyl-1-decanoate-4-decanoate	Niacinamide
Example 48.	1,2,3,4-butantetraol-2-(2-methyl-octanoate)	Niacinamide
Example 49.	1,2,3,4-butantetraol-1-hexanoate-2-hexanoate	Aminoniacinamide
Example 50.	Glyceryl-2-(3,5,7-hexadecatrienoate)	Thioniacinamide

Examples 51 to 60: Molar ratio Fatty acid mono- or di-esters of a polyhydric hydroxyalkane/ pyridine carboxy derivative 2:7 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 2 mol.	Pyridine carboxy derivative 7 mol.
Example 51.	Glyceryl-1-octanoate	Niacinamide
Example 52.	Glyceryl-2-octanoate	Niacinamide

Example 53.	Glyceryl-1-heptanoate	Aminoniacinamide
Example 54.	Glyceryl-1-octanoate-2-octanoate	Thioniacinamide
Example 55.	Glyceryl-2-(3,5,7-hexadecatrienoate)	N2-methyl-niacinamide
Example 56.	Glyceryl-1-(3-ethyl-2-methyl-8,10-eicosadienoate)- 2-octanoate	Aminoniacinamide
Example 57.	Propylenglycyl-1-(2,4-ethyl-6-tetradecaenoate)-2-(8,12-hexadecaenoate)	Thioniacinamide
Example 58.	1,2-butylenglycyl-1-decanoate	N2-methyl-niacinamide
Example 59.	1,2-butylenglycyl-1-heptadecanoate-2-(4,8-heptadecadienoate)	Niacinamide
Example 60.	1,2-butylenglycyl-1-(8-ethyl-4-methyl-6,16-octadecadienoate)	Thioniacinamide

Examples 61 to 70: Molar ratio Fatty acid mono- or di-esters of a polyhydric hydroxyalkane/ pyridine carboxy derivative 1:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 1 mol,	Pyridine carboxy derivative 1 mol.
Example 61.	Glyceryl-1-(5,8,11,14,17-eicosapentaenoate)	Niacinamide
Example 62.	Propylenglycyl-1-nonanoate-2-decanoate	Thioniacinamide
Example 63.	Trimethylenglycyl-1-octanoate-2-(4-ethyl-decanoate)	N2-methyl-niacinamide
Example 64.	1,3-butylenglycyl-1-undecanoate	N2-ethyl-niacinamide
Example 65.	1,3-butylenglycyl-3-hexanoate	Thioniacinamide
Example 66.	1,3-butylenglycyl-1-octanoate-3-octanoate	Aminoniacinamide
Example 67.	1-ol-2,3-butylenglycyl-1-undecanoate-2-undecanoate	Niacinamide
Example 68.	1-ol-2,3-butylenglycyl-1-(2-ethyl-nonanoate)-2-hexanoate	Thioniacinamide
Example 69.	Glyceryl-2-octanoate	N2-methyl-niacinamide
Example 70.	Glyceryl-1-octanoate-2-octanoate	N2-ethyl-niacinamide

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Examples 71 to 80: Molar ratio Fatty acid mono- or di-esters of a polyhydric hydroxyalkane/ pyridine carboxy derivative 5:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 5 mol.	Pyridine carboxy derivative 1 mol.
Example 71.	1,4-butylenglycyl-1-octanoate-4-heptanoate	Thioniacinamide
Example 72.	2,3-butylenglycyl-2-dodecanoate-3-heptanoate	Aminoniacinamide

Example 73.	1,2,3,4-butantetraol-2-(2-methyl-octanoate)	Niacinamide
Example 74.	1,2,3,4-butantetraol-1-hexanoate-2-hexanoate	Thioniacinamide
Example 75.	1,4-butylenglycyl-1-(6,10,12,18-tetradecantetraenoate)-4-(4,8-dimethyl-6,13-eicosadienoate)	N2-methyl-niacinamide
Example 76.	1,4-butylenglycyl-1-(2-ethyl-octanoate)-4-(4-nonenoate)	N2-ethyl-niacinamide
Example 77.	Glyceryl-1-octanoate	Thioniacinamide
Example 78.	Glyceryl-1-(5,8,11,14,17-eicosapentaenoate)	Aminoniacinamide
Example 79.	Glyceryl-2-(8,11,14-eicosatrienoate)	Niacinamide
Example 80.	1,2,3,4-butantetraol-2-(2-methyl-octanoate)	Niacinamide

Examples 81 to 85: Molar ratio Fatty acid mono- or di-esters of a polyhydric hydroxyalkane / pyridine carboxy derivative 50:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 50 mol.	Pyridine carboxy derivative 1 mol.
Example 81.	Ethyleneglycyl-1-octanoate	Thioniacinamide
Example 82.	Ethylenglycyl-1-octanoate-4-(3-ethyl-hexanoate	Aminoniacinamide
Example 83.	Glyceryl-1-octanoate	Niacinamide
Example 84.	Glyceryl-1-(5,8,11,14,17-eicosapentaenoate)	Thioniacinamide
Example 85.	Glyceryl-2-(8,11,14-eicosatrienoate)	N2-methyl-niacinamide

Examples 86 to 90: Molar ratio Fatty acid mono- or di-esters of a polyhydric hydroxyalkane / pyridine carboxy derivative 500:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 500 mol.	Pyridine carboxy derivative 1 mol.
Example 86.	Glyceryl-2-(8,11,14-eicosatrienoate)	Thioniacinamide
Example 87.	1,2,3,4-butantetraol-2-(2-methyl-octanoate)	Aminoniacinamide
Example 88.	Glyceryl-1-octanoate	Niacinamide
Example 89.	Trimethylenglycyl-2-(4-methyl-2,8-eicosadienoate)	Thioniacinamide
Example 90.	Propylenglycyl-1-nonanoate	N2-methyl-niacinamide

Examples 91 to 96: Molar ratio Fatty acid mono- or di-esters of a polyhydric hydroxyalkane / pyridine carboxy derivative 1000:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 1000 mol.	Pyridine carboxy derivative 1 mol.
Example 91.	Glyceryl-1-(5,8,11,14,17-eicosapentaenoate)	Thioniacinamide
Example 92.	Propylenglycyl-1-(2,4-ethyl-6-tetradecaenoate)-2-(8,12-hexadecaenoate)	Aminoniacinamide
Example 93.	1,2-butylenglycyl-1-decanoate	Niacinamide
Example 94.	1,2-butylenglycyl-2-octanoate	Thioniacinamide
Example 95.	Glyceryl-2-octanoate	N2-methyl-niacinamide
Example 96.	1,4-butylenglycyl-1-decanoate-4-decanoate	N2-ethyl-niacinamide

Examples 97 to 100: Molar ratio Fatty acid mono- or di-esters of a polyhydric hydroxyalkane / pyridine carboxy derivative 10000:1 (mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 10000 mol.	Pyridine carboxy derivative 1 mol.
Example 97.	Glyceryl-2-octanoate	Thioniacinamide
Example 98.	Ethylenglycyl-1-decanoate-2-hexanoate	Aminoniacinamide
Example 99.	1-ol-2,3-butylenglycyl-1-(2-ethyl-nonanoate)-2-hexanoate	Niacinamide
Example 100.	Glyceryl-2-(8,11,14-eicosatrienoate)	Thioniacinamide

General method examples 101-110:

A lotion with a quantity of the Fatty acid mono- or di-esters of a polyhydric hydroxyalkane and the pyridine carboxy derivative are made.

A lotion of the following composition (w/w) % are made

Water:	59.9%
Complex:	5.0%
Methylparaben:	0.1%
Tefose 63:	12.0%
Arachis oil:	10.0%
Isopropylmyristat (16):	10.0%
Sodium stearoyl lactylate:	2.0%

Examples 101 to 103: 100 g lotion comprising 5% (w/w) of a complex comprising a fatty acid mono- or di-ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative in a weight ratio of 1:2 (w/w).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 1.665g	Pyridine carboxy derivative 3.335g
Example 101.	Glyceryl-2-octanoate 1.665g	Thioniacinamide 3.335g
Example 102.	Glyceryl-2-(8,11,14-eicosatrienoate) 1.665g	Aminoniacinamide 3.335g
Example 103.	Ethylenglycyl-1-decanoate-2-hexanoate 1.665g	N2-ethyl-niacinamide 3.335g

Examples 104 to 106: 100 g lotion comprising 10% (w/w) of a complex comprising a fatty acid mono- or di-ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative in a weight ratio of 1:2 (w/w).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane 3.333g	Pyridine carboxy derivative 6.667g
Example 104.	Glyceryl-1-octanoate-2-octanoate 3.333g	Thioniacinamide 6.667g
Example 105.	Glyceryl-1-(5,8,11,14,17-eicosapentaenoate) 3.333g	Aminoniacinamide 6.667g
Example 106.	Glyceryl-2-(8,11,14-eicosatrienoate) 3.333g	N2-ethyl-niacinamide 6.667g

Examples 107 to 110: 500 g lotion comprising 5% (w/w) of a complex comprising a fatty acid mono- or di-ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative in a molar ratio of 2:7(mol/mol).

	Fatty acid mono- or di-esters of a polyhydric hydroxyalkane	Pyridine carboxy derivative
Example 107.	Glyceryl-2-octanoate 218.3g/mol	Niacinamide 122.13g/mol

	8.451g	16.549g
Example 108.	Ethyleneglycyl-1-hexanoate 160.21g/mol 6.221g	Thioniacinamide 138.19g/mol 18.779g
Example 109.	1,3-butyleneglycyl-3-hexanoate 188.27g/mol 7.043g	Aminoniacinamide 137.14g/mol 17.957g
Example 110.	Glyceryl-1-octanoate-2-octanoate 328.5g/mol 10.864g	Niacinamide 122.13g/mol 14.136g

Example 111

Investigation of the therapeutic effect of a complex of a fatty acid ester of a polyhydric hydroxyalkanes and a pyridine carboxy derivative..

Objective

The objective of this study was to assess the therapeutic effect of a dose of an ester according to the invention compared to a clinically relevant dose of the topical glucocorticosteroid hydrocortisone. All compounds were administered topically in the TPA induced ear inflammation test model in the mouse, a commonly employed method for screening and evaluation of anti-inflammatory drugs.

Test articles and vehicle

The test article is the complex prepared according to example 51 (Compound 51 in the following). All substances were obtained from Astion A/S, Denmark.

Animals

The study was performed in female BALB/ca mice from M & B A/S, DK-8680 Ry. At start of the acclimatisation period the mice were in the weight range of 20 g (+/- 5g).

Housing

The study took place in an animal room provided with filtered air. The temperature in the room was set at 21 - 23°C and the relative humidity to ≥30%. The room was illuminated to give a cycle of 12 hours light and 12 hours darkness. Light was on from 06.00 till 18.00 h.

The animals were housed in Macrolon type III cages (40x25x14 cm), 10 in each cage. The cages were cleaned and the bedding changed at least once a week.

Bedding

The bedding was sawdust (Tapvei 4HV) from Tapvei Oy, 73620 Kortteinen, Finland.

Diet

A complete pelleted rodent diet "Altromin 1324" from Chr. Petersen, DK- 4100 Ringsted, was available ad libitum.

Drinking water

The animals had free access to bottles with domestic quality drinking water. The drinking water was changed daily.

Animal randomisation and allocation

On the day of arrival the animals were randomly allocated to groups of 10 mice.

Body weight

The animals were weighed on the day of dosing and termination of the study.

Procedure

The test substances were administered 20 minutes before and 20 minutes after application of TPA to the ear.

All groups were treated with 20µl TPA solution 400 µg/ml in acetone, on the right ear.

The doses were as follows:

Drug	Dose, mg/ear
Vehicle, PBS	-
Compound 51	1.00
Compound 51	3.00
Betamethasone 17-valerate	0.02

Three hours after the TPA application the mice were sacrificed, the ears cut from the tip with a punch biopsy knife (8 mm diameter) and weighed.

Mean weights and standard deviations were calculated. Relative ear oedema was assessed as the weight difference between right and left ear of each mouse expressed as percent of the left ear. Percent inhibition of the relative ear oedema compared with the vehicle

treated groups was calculated for the test substance and reference compound treated groups.

Clinical signs

All visible signs of ill health and any behavioural changes were recorded daily during the study. Any deviation from normal was recorded with respect to time of onset, duration and intensity.

Statistics

Differences in relative ear oedema between the vehicle treated group and the other groups were tested for significance employing a non-parametric statistical method of analysis, the Mann-Whitney U test. The required level of significance will be $p<0.05$.
All statistical analysis was performed employing the statistical software package Analyse-it v. 1.62.

RESULTS

Clinical signs

TPA caused an inflammation in the right ears, which was visible after about 30 minutes. It could clearly be observed that the right ears were bright red and the left ears pale. The test articles to some extent prevented the reaction in the right ear. No test substance related adverse reactions were observed.

Ear oedema

The various concentrations of the test articles inhibited the relative oedema as shown in the table below:

Drug	Dose, mg/ear	% Inhibition of relative ear oedema	Mann-Whitney U test
Vehicle, PBS	-	-	-
Compound 51	1.00	62	p=0.001
Compound 51	3.00	85	P<0.0001
Betamethasone 17-valerate	1.00	95	P<0.0001

Compound 51 yielded a statistically significant and dose dependent inhibition of ear oedema comparable to the effect of betamethasone 17-valerate which was applied at a clinically relevant dose level.

CONCLUSION

The data shows that Compound 51 is a potent inhibitor of TPA induced ear oedema and that the effect was comparable to a clinically relevant dose of the strong steroid betamethasone 17-valerate.

Example 112

Objective

The objective of this study was to assess the antimicrobial effect of a complex of the invention and the corresponding doses of its components in a number of pathogenic bacteria and fungi.

Test articles and vehicle

The test articles are the complex prepared according to example 51 (Compound 51 in the following) and its components Glyceryl-1-octanoate and niacinamide. All substances were obtained from Astion A/S, Denmark.

Experimental procedure

Test substance or vehicle is added to test wells containing the selected microorganisms ($1x10^4$ to $5x10^5$ CFU/ml)in cultures grown under controlled conditions.The final innoculum concentration is determined by reference to a standard optical density curve and adjusted as required. After 1 to 4 days, growth of the culture is examined and scored positive (+) for inhibition of growth or turbidity, or negative (-) for no effect upon growth or turbidity. An initial test concentration of 3 mM in 1% DMSO is used and dilutions are tested to establish the minimal inhibitory concentration (MIC).

Results

The substances are administered so that the molar concentration of the complex is directly comparable to the molar concentration of the components of the complex.
The following table shows the MIC obtained for each substance:

Organism	Compound 51	Glyceryl-1-octanoate	Niacinamide
Candida albicans	300 µM	Not active	Not active
Epidermophyton floccosum	1000 µM	Not active	Not active
Microsporum canis	1000 µM	Not active	Not active
Streptococcus faecalis	3 mM	Not active	Not active
Trichophyton rubrum	1000 µM	Not active	Not active

Conclusion

The data clearly show that the complexes of the invention are superior to the corresponding doses of their individual components, since the complexes displayed clear anti-fungal and anti-bacterial effects, while the components were without effect at the same doses. This clearly demonstrates a synergistic effect of the complex of the invention.

Example 113

Objective

The objective of this study was to assess the antibacterial effect of a complex of the invention against a mithicillin resistant bacteria strain.

Test articles and vehicle

The test articles are the complex prepared according to example 51 (Compound 51 in the following). All substances were obtained from Astion A/S, Denmark.

Experimental procedure

Test substance or vehicle is added to test wells containing the selected microorganisms ($1x10^4$ to $5x10^5$ CFU/ml)in cultures grown under controlled conditions.The final innoculum concentration is determined by reference to a standard optical density curve and adjusted as required. After 1 to 4 days, growth of the culture is examined and scored positive (+) for inhibition of growth or turbidity, or negative (-) for no effect upon growth or turbidity. An initial test concentration of 3 mM in 1% DMSO is used and dilutions are tested to establish the minimal inhibitory concentration (MIC).

Results

The substances are administered so that the molar concentration of the complex is directly comparable to the molar concentration of the components of the complex.
The following table shows the MIC obtained for each substance:

Organism	Compound 51
Staphylococcus aureus	1000 µM
Staphylococcus aureus Methicillin Resistant	300 µM

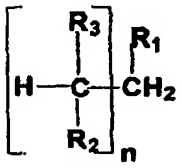
Conclusion

The data clearly show that the complex of the invention has a convincing inhibiting effect on Staphylococcus aureus. Furthermore it is observed that complex is even more effective against the Mithicillin resistant strain, where many existing antibiotics typically show weaker activity against resistant strains.

CLAIMS

1. A chemical complex comprising:

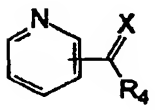
i) a fatty acid ester of a polyhydric hydroxyalkane according to formula I;



I

wherein n is 1, 2, 3, 4 or 5, at least one of the R_1, R_2 and R_3 is OOR' and at most two of the R_1, R_2 and R_3 is independently selected from H, OH, OM and OOR', wherein R' is selected from C_6-C_{20} alkyl and C_6-C_{20} alkenyl and isomers thereof; and OM is a salt; and

ii) an optionally substituted pyridine carboxy derivative or salts thereof according to formula II



II

wherein X is selected from O and S; R_4 is selected from OH; OR''; NH_2; NHR''; NR''R'''; O^-Y^+, and halogen, wherein R'' and R''' are independently selected from optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} alkoxyl and optionally substituted C_2-C_{20} alkenyl; and Y is a base addition salt of the free carboxylate.

2. The complex according to claim 1, wherein the R' is selected from C_6-C_{14} alkyl and C_{14}-C_{20} alkenyl and isomers thereof.

3. The complex according to any one of the preceding claims, wherein said n is 1, 2 or 3.

4. The chemical complex according to any one of the preceding claims, wherein at least one of the R_1, R_2 and R_3 is OH.

5. The chemical complex according to any one of the preceding claims, wherein at most two of the R_1, R_2 and R_3 is OOR'.

6. The chemical complex according to any one of the preceding claims, wherein the OOR' is selected from the group consisting of caproic acid, caprylic acid, capric acid, lauric acid or n-myristic acid moieties.

7. The chemical complex according to any one of the preceding claims, wherein the pyridine carboxy derivative is pyridine-3-carboxy derivative.

8. The chemical complex according to any one of the preceding claims, wherein the R" and the R"' are independently selected from optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} alkoxyl and optionally substituted C_1-C_{10} alkenyl.

9. The chemical complex according to any one of the preceding claims, wherein the R" and the R"' are independently selected from optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C6 alkoxyl and optionally substituted C_1-C_6 alkenyl.

10. The chemical complex according to any one of the preceding claims, wherein R" and R"' are independently selected from optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 alkoxyl and optionally substituted C_1-C_4 alkenyl.

11. The chemical complex according to any one of the preceding claims, wherein said optional substitution of said pyridine carboxy derivative include substitution of one or more hydrogen atoms with a chemical group selected from the group consisting of carboxyl, formyl, amino, hydroxyl, halogen, nitro, sulphono, sulphanyl, C_1-C_6-alkyl, mono- and di(C_1-C_6-alkyl)amino and alkoxy.

12. The chemical complex according to any one of the preceding claims, wherein the pyridine carboxy derivative is selected from the group consisting of niacinamide, thioniacinamide, 6-aminoniacinamide, N2-methyl-niacinamide, N2-ethyl-niacinamide, nicotinic acid, inositol hexaniacinate 6-methoxy-niacinamide and salts thereof.

13. The chemical complex according to any one of the preceding claims, wherein the pyridine carboxy derivative is selected from the group consisting of niacinamide, thioniacinamide, 6-aminoniacinamide, N2-methyl-niacinamide, N2-ethyl-niacinamide and salts thereof.

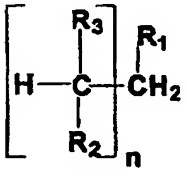
14. The chemical complex according to any one of the preceding claims, wherein the pyridine carboxy derivative is niacinamide.

15. The chemical complex according to any one of the preceding claims, wherein the fatty acid ester of a polyhydric hydroxyalkane and the pyridine carboxy derivative are present in a molar ratio of between about 1:10000 to 10000:1, preferably about 1:1000 to 1000:1, more preferably of about 1:100 to 100:1, even more preferably of about 1:10 to 10:1, most preferably of about 1:5 to 5:1 or about 1:2 to 2:1.

16. The chemical complex according to any one of the preceding claims, wherein the fatty acid ester of a polyhydric hydroxyalkane and the optionally substituted pyridine carboxy derivative are present in a mass ratio of between about 1:10000 to 10000:1, preferably about 1:1000 to 1000:1, such as about 1:100 to 100:1, such as about 1:10 to 10:1, also about 1:5 to 5:1, such as about 1:2 to 2:1.

17. A composition comprising:

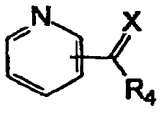
i) A fatty acid ester of a polyhydric hydroxyalkane according to formula I;



I

wherein n is 1, 2, 3, 4 or 5, at least one of the R_1, R_2 and R_3 is OOR' and at most two of the R_1, R_2 and R_3 is independently selected from H, OH, OM and OOR', wherein R' is selected from C_6-C_{20} alkyl and C_6-C_{20} alkenyl and isomers thereof; and OM is a salt; and

ii) an optionally substituted pyridine carboxy derivative or salts thereof according to formula II



II

wherein X is selected from O and S; R_4 is selected from OH; OR"; NH_2; NHR"; NR"R"', O^-Y^+, and halogen, wherein R" and R"' are independently selected from optionally substituted C_1-C_{20} alkyl, optionally substituted C_1-C_{20} alkoxyl and optionally substituted C_2-C_{20} alkenyl; and Y is a base addition salt of the free carboxylate.

18. The composition according to claim 17, further comprising one or more excipient(s) or carrier(s).

19. The composition according to any one of claims 17 or 18, wherein the R' is selected from C_6-C_{14} alkyl and C_{14}-C_{20} alkenyl and isomers thereof.

20. The composition according to any one of claims 17 to 19, wherein said n is 1, 2 or 3.

21. The composition according to any one of claims 17 to 20, wherein at least one of the R_1, R_2 and R_3 is OH.

22. The composition according to any one of claims 17 to 21, wherein at most two of the R_1, R_2 and R_3 is OOR'.

23. The composition according to any one of claims 17 to 22, wherein the OOR' is selected from the group consisting of caproic acid, caprylic acid, capric acid, lauric acid or n-myristic acid moieties.

24. The composition according to any one of claims 17 to 23, wherein the pyridine carboxy derivative is pyridine-3-carboxy derivative.

25. The composition according to any one of claims 17 to 24, wherein the R" and the R"' are independently selected from optionally substituted C_1-C_{10} alkyl, optionally substituted C_1-C_{10} alkoxyl and optionally substituted C_1-C_{10} alkenyl.

26. The composition according to any one of claims 17 to 25, wherein the R" and the R"' are independently selected from optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C6 alkoxyl and optionally substituted C_1-C_6 alkenyl.

27. The composition according to any one of claims 17 to 26, wherein R" and R"' are independently selected from optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 alkoxyl and optionally substituted C_1-C_4 alkenyl.

28. The composition according to any one of claims 17 to 27, wherein said optional substitution of said pyridine carboxy derivative include substitution of one or more hydrogen atoms with a chemical group selected from the group consiting of carboxyl, formyl, amino, hydroxyl, halogen, nitro, sulphono, sulphanyl, C_1-C_6-alkyl, mono- and di(C_1-C_6-alkyl)amino and alkoxy.

29. The composition according to any one of claims 17 to 28, wherein the pyridine carboxy derivative is selected from the group consisting of niacinamide, thioniacinamide, 6-aminoniacinamide, N2-methyl-niacinamide, N2-ethyl-niacinamide, nicotinic acid, inositol hexaniacinate 6-methoxy-niacinamide and salts thereof.

30. The composition according to any one of claims 17 to 29, wherein the pyridine carboxy derivative is selected from the group consisting of niacinamide, thioniacinamide, 6-aminoniacinamide, N2-methyl-niacinamide, N2-ethyl-niacinamide and salts thereof.

31. The composition according to any one of claims 17 to 30, wherein the pyridine carboxy derivative is niacinamide.

32. The composition according to any one of claims 17 to 31, wherein the combination of the fatty acid ester of a polyhydric hydroxyalkane and the pyridine carboxy derivative are present in a molar ratio of between about 1:10000 to 10000:1, preferably about 1:1000 to 1000:1, more preferably of about 1:100 to 100:1, even more preferably of about 1:10 to 10:1, most preferably of about 1:5 to 5:1 or about 1:2 to 2:1.

33. The composition according to any one of claims 17 to 31, wherein the combination of the fatty acid ester of a polyhydric hydroxyalkane and the optionally substituted pyridine carboxy derivative are present in a mass ratio of between about 1:10000 to 10000:1, preferably about 1:1000 to 1000:1, such as about 1:100 to 100:1, such as about 1:10 to 10:1, also about 1:5 to 5:1, such as about 1:2 to 2:1.

34. A composition comprising a complex as defined in any one of claims 1 to 16.

35. The composition according to claim 34, further comprising one or more excipient(s) or carrier(s).

36. The composition according to any one of claims 17 to 35 further comprising one or more therapeutically active agents.

37. The composition according to any one of claims 17 to 36 formulated as a pharmaceutical composition for oral, topical, transdermal, or parenteral administration.

38. The composition according to claim 37 formulated as a pharmaceutical composition for oral or topical administration.

39. The composition according to any one of claims 17 to 35 for use as a dietary supplement.

40. The composition according to any one of claims 17 to 35, 37 and 38 for use as a cosmetic.

41. A use of a combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative for the preparation of a medicament for the immunomodulation of a mammal, such as a human.

42. A use of a combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative for the preparation of a medicament for anti-microbial treatment of a mammal, such as a human.

43. The use according to any one of claims 41 or 42, wherein the medicament comprises a composition as defined in any one of claims 17 to 38 or a complex as defined in any one of claims 1 to 16.

44. The use according to any one of claims 41 or 42, wherein the combination of the fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative is a chemical complex as defined in any one of claims 1 to 16.

45. The use according to claim 40, wherein the immunomodulation is selected from the group of suppression of hypersensitivity and suppression of inflammatory reactions.

46. The use according to claim 41, wherein the anti-microbial treatment is selected from the group consisting of bactericidal, fungicidal, antiviral and anti-parasital treatment.

47. The use according to claim 40, wherein the immodulation is associated with diseases and disorders selected from the group consisting of hypersensitivity skin disease, pruritus, urticaria, atopic eczema, contact dermatitis, seborrhoeic dermatitis, acne, rosacea, alopecia, vitiligo, psoriasis IgE mediated allergic reactions, asthma, allergic rhinitis,

anaphylaxis, autoimmune disease, chronic inflammatory disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout, osteoarthritis, pain and cancer.

48. The use according to any one of claims 40 to 47, wherein the fatty acid ester of a polyhydric hydroxyalkane and the pyridine carboxy derivative are together comprised in a single formulation or are each individually comprised in separate formulations.

49. The use according to any one of claims 40 to 48, wherein the combination of a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative is administered by means of oral, topical, transdermal, or parenteral administration, or combinations thereof.

50. The use according to any one of claims 40 to 49, wherein the medicament further comprises one or more therapeutically active agents.

51. The use according to claim 48, wherein the separate formulations are administered in a simultaneous or non-simultaneous manner.

52. The use according to any one of claims 49 or 50, wherein the fatty acid ester of a polyhydric hydroxyalkane and the pyridine carboxy derivative are together comprised in a single formulation.

53. A method for immunomodulation in a mammal, such as a human, comprising the administration to said mammal an effective amount of a combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative, or a chemical complex comprising a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative.

54. A method for the suppression of bacteria, fungi, vira or parasites in a mammal, such as a human, comprising the administration to said mammal an effective amount of a combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative, or pharmaceutically acceptable salts thereof, or a chemical complex comprising a fatty acid ester of a polyhydric hydroxyalkane and a pyridine carboxy derivative, or pharmaceutically acceptable salts thereof.

55. The method according to claim 53, wherein the immunomodulation is treatment of hypersensitivity and/or inflammatory diseases or conditions.

56. The method according to claim 53, wherein the immunomodulation is treatment of hypersensitivity skin reaction or skin disease.

57. The method acording to claim 53 for the treatment of pruritus, urticaria, atopic eczema, contact dermatitis, seborrhoeic dermatitis, acne, rosacea, alopecia, vitiligo and/or psoriasis .

58. The method according to claim 53, wherein the immunomodulation is treatment of IgE mediated allergic reaction and/or condition.

59. The method according to claim 58, for the treatment of asthma, allergic rhinitis, and/or anaphylaxis .

60. The method according to claim 53, wherein the immunomodulation is treatment of autoimmune disease and/or chronic inflammatory disease.

61. The method according to claim 60 for the treatment or prevention of diabetes, Crohn's disease, ulcerative colitis, rheumatoid arthritis, gout or osteoarthritis.

62. The method according to claim 53, wherein the immunomodulation is alleviation of pain.

63. The method according to claim 53, wherein the immunomodulation is for the treatment of cancer.

64. The method according to claim 31, wherein the combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative is a chemical complex as defined in claims 1 to 6.

65. The method according to claims 31, wherein the combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative, or pharmaceutically acceptable salts thereof, are together comprised in a single formulation or are each individually comprised in separate formulations.

66. The method according to claim 31, wherein the combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative is administered by means of oral, topical, transdermal, or parenteral administration, or combinations thereof.

67. The method according to claim 31, wherein the separate formulations are administered in a simultaneous or non-simultaneous manner.

68. The method according to claim 31, wherein the separate formulations further comprises one or more therapeutically active substances.

69. The method according to claim 43, wherein the combination of a fatty acid ester of a polyhydric hydroxyalkane and an optionally substituted pyridine carboxy derivative are together comprised in a single formulation.

70. The method according to claim 47, wherein the single formulation further comprises one or more therapeutically active substances.